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Perspectives and Commentaries

Interferons and Cell Growth Regulation

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ALTHOUGH interferon was discovered in 1958, it has only been during the past decade that the multitude of biologic effects of interferon have been disclosed. More recently, notable advances in molecular biology have resulted in an accurate description of the amino acid sequence, coding genes and chromosomal assignment of all three major types and most subtypes of interferons, a unique accomplishment in the study of a human protein.

This interest originated from the broad spectrum of biologic activities displayed by these molecules and their potential as therapeutic agents for viral and malignant diseases. If one is to attempt a generalization of these biologic activities, interferons are, in essence, cell growth regulatory molecules. In this context, interferons have been compared to classical peptide hormone systems because they are produced *de novo* by differentiated cells upon stimulation by a variety of inducers and its eventual activity on the target cells occurs via specific cell membrane receptors. Like hormones, the interferon system participates in the regulation of cell growth and differentiation [1].

Interferons are potent cell growth inhibitors, but the biochemical events that mediate such activity are poorly understood. The existence of second messengers conveying signals originating from the cell membrane upon interaction of interferon and its receptors have been postulated. Cyclic nucleotides have been associated with the antiproliferative effects (and antiviral activity) but its role in mediating such activity remains largely controversial [2].

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Distinct enzyme systems have been implicated in the mechanisms of action: (1) Sreevalsan *et al.* [3] have found that interferon selectively inhibits the activation of ornithine decarboxylase, a key enzyme in polyamine synthesis, and have related this to growth inhibition; (2) a deficiency of fatty acid cyclo-oxygenase activity has been found in cells becoming resistant to the growth inhibitory activity of interferon, suggesting a role for this enzyme as a mediator molecule [4]; and (3) the induction of 2′–5′oligoisoadenyl synthetase, one of the described mediators of the antiviral activity, has also been associated with the antiproliferative activity, but conflicting data on this subject abound [2]. It is clear, however, that growth inhibition can occur via inhibition of the synthesis of viral-induced proteins that favor cell multiplication, or by a direct antiproliferative effect which is unaltered by inhibitors of the antiviral activity.

Recently, Inglot [1] has shown antagonistic effects of interferons with various cell growth factors, suggesting that cellular proliferation may be regulated by opposing actions between growth-promoting factors and interferons. She has also demonstrated that proliferation of certain cell lines can be stimulated by low doses of interferon, and has postulated that this effect may be actually due to facilitation of growth-promoting factor(s) activity. Conceivably, a delicate balance between growth stimulators and interferons regulates the complex signaling which directs cell growth. Such balance seems to depend on molecules acting on the cell membrane, with fine thresholds, whereby a low dose of a given factor may activate or facilitate the activity of the opposing factor. In addition to physiologic growth factors, transforming growth

factors sustaining growth of tumor cells and virus-derived growth-promoting proteins in cells transformed by retroviruses have been discovered [5]. In the malignant cell the activity of these molecules may be dependent on the ability of interferon to control or modulate the expression of oncogenes governing abnormal proliferation. The finding by Lin *et al.* [6] that interferon suppresses the expression of the protein product of the src gene (pp60), which regulates growth of the transformed cells, supports this contention.

The study of Ludwig *et al.* provides interesting evidence that interferons may also enhance growth of malignant cells of diverse origin. Using an agar-based human tumor clonogenic assay, they found that 7% of the tumor samples studied seem to show growth stimulation when cultured in the presence of partially pure or recombinant DNA-derived interferon alpha. The origin of the tumor and the dose of interferon were important variables in these experiments. Stimulation of cell growth occurred when low doses of interferon were used and the phenomenon occurred more frequently in samples derived from patients with acute myelogenous leukemia. In this regard the tumor clonogenic assay only measures the most direct effect of interferon but does not account for other biologic activities, such as activation of immune cytotoxic functions *in vivo* [7], which may be relevant in controlling malignant cell growth, especially those of hematologic origin. The human tumor clonogenic assay has been shown to be adequate in identifying cytotoxic drugs to which a tumor is resistant, but the ability to predict other events awaits further sophistication of the method [8].

Shortly after the purification of alpha interferon by Cantell *et al.* [9] and the description of its antitumor activity [10], the first reports describing tumor regression in cancer patients followed [11–13]; this led to exceptional interest in this family of proteins. As of today, there is no direct evidence to suggest that interferon promotes tumor growth in cancer patients. However, 'mixed effects' in patients with renal cancer receiving interferon alpha in whom regression of metastatic tumors occurred, while others continued to grow, have been reported [14]. It is unknown whether the lesions that continued to grow were enhanced by interferon, but this clinical observation indicates that clonal heterogeneity of the tumor may be a crucially important variable when cells are grown *in vitro*. Other physiologic variables, determining the tissue concentration of interferon in a given organ or tumor, will result in different amounts of interferon interacting with the hormonal milieu of the cells involved, therefore possibly determining the nature of the *in vivo* response of the target cells.

Ludwig's report will stimulate clinicians to look critically at this or similar *in vitro* tests of drug activity for interferons. The design of future clinical studies with interferons will likely benefit by incorporating tests aimed to predict events *in vivo*.

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